Express Mail Label No.: EV392158323US
Date of Deposit: December 23, 2004 **Attorney Docket No. 28856-501**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S): Hangauer *et al.*

SERIAL NUMBER: 09/482,585 EXAMINER: P. Ponnaluri

FILING DATE: January 13, 2000 ART UNIT: 1639

FOR: A NOVEL METHOD FOR DESIGNING PROTEIN KINASE INHIBITORS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Boston, Massachusetts
December 23, 2004

DECLARATION UNDER 37 C.F.R. §1.132

I, David Hangauer, Jr., hereby declare and state as follows:

1. I, along with Thomas H. Marsilje and Karen L. Milkiewicz, am one of the named inventors of the claimed inventions in the above-identified patent application. I received my B.S. degree in Chemistry from Canisius College, Buffalo, NY in 1974. I received my Ph.D. in the field of Chemistry from The University at Buffalo, The State University of New York in 1980. I have been working in the field of Medicinal Chemistry since 1980, and working with protein kinase inhibitors since 1984.

2. I have read, and am familiar with, the contents of the United States patent application entitled "A Novel Method for Designing Protein Kinase Inhibitors", serial number 09/482,585, which was filed January 13, 2000. I understand that the pending claims are directed to methods for identifying inhibitors of protein kinases.

3. I am aware that the Examiner has issued a non-final Office Action, mailed on June 23, 2004 in the above-identified application ("the Application"). I am aware that the Examiner has rejected the pending claims (*i.e.*, claims 1, 3-8, 13-20 and 22) under 35 U.S.C. §112, first paragraph as lacking adequate written description and enablement and under 35 U.S.C. §112, second paragraph as being indefinite.

4. I make this declaration to rebut the Examiner's rejections, with which I do not agree. In view of the express statements in the specification regarding methods of identifying inhibitors of

protein kinases and the voluminous experimental evidence that has been accumulated, in my opinion, the ordinarily skilled artisan would be able to routinely perform the described methods with a reasonable expectation of successfully identifying suitable kinase inhibitors. I am also of the opinion that the ordinarily skilled artisan would believe that such method of identifying kinase inhibitors is a directed, rational, and more efficient method than methods known in the art at the time the invention was made.

5. Protein kinases are enzymes that use two substrates simultaneously, 1) a peptide/protein with an amino acid side chain hydroxyl group (OH) that becomes phosphorylated and 2) adenosine triphosphate (ATP) that donates the phosphate. The products of the reaction are then a peptide/protein phosphate and adenosine diphosphate (ADP). Prior to this invention, and the vast majority of the ongoing efforts in the pharmaceutical industry have been focused on small molecule, non-peptide, inhibitors that bind in *the same* binding pocket as ATP. The present invention provides a method for discovering small molecule, non-peptide, *non-ATP competitive* inhibitors (*i.e.* those that do not bind in the ATP binding pocket).

6. This invention is a novel, rational, directed method for discovering small molecules that are inhibitors of protein kinases. This method involves *in silico* design of inhibitors (*e.g.*, using molecular modeling steps) based on structural information of the kinase active site and known peptide substrates and inhibitors, in combination with *in vitro* assay techniques to design effective kinase inhibitors in a modular fashion. Further, the method produces non-peptide inhibitors with minimal structural complexity, meaning that the structure of the inhibitors are only as complex as needed to achieve the desired biological objectives, but not more; good oral drug properties relative to peptide inhibitors; allows efficient screening of large numbers of compounds and produces a much higher percentage of active compounds relative to random or maximum diversity combinatorial library design. Finally, the more kinase targets the method is applied to, the more efficient it becomes. The invention is described in detail in Appendix A.

7. Applicants expressly provided ample guidance in the specification about how to perform the methods of the invention. The use of initial molecular modeling studies to model candidate

first module (M_1) functional groups in the conserved catalytic region of the serine kinase cAMP-dependent protein kinase ("PKA") active site (see Figure 3 and page 11, line 1 to page 13, line 9) and the subsequent formation of specific pentapeptide-based inhibitors which include an M_1 functional group covalently bound to a pentapeptide sequence, based on initial modeling studies for PKA and $pp60^{c\text{-}Src}$ (page 13, line 10 to page 22, line 7 of the specification).

8. Applicants provided examples of using two different pentapeptide scaffolds in the method, including: (1) Ac-Arg-Arg-Gly-Xaa-Ile-NH_2 (see Table I), and (2) Ac-Ile-Xaa-Gly-Glu-Phe-NH_2 (see Table II). The Xaa in the first sequence is Ala covalently bonded to an M_1. The Xaa in the second sequence is Phe covalently bonded to an M_1. As shown in Table I of the specification, eleven (11) different functional groups for M_1 were tested and as shown in Table II, eight (8) different functional groups for M_1 were tested, including, but not limited to, phosphonic acid, sulfamic acid, carboxylic acid, aldehyde, and amide functional groups.

9. Additional peptide scaffolds for specific protein kinase inhibitors which can be used as starting materials in the method of the present invention are known in the art and are described, for example, in Pearson et al., "Protein Kinase Phosphorylation Site Sequences and Consensus Specificity Motifs: Tabulations," Methods in Enzymology 200:62-81 (1991); Kemp et al., "Design and Use of Peptide Substrates for Protein Kinases," Methods in Enzymology 200:121-134 (1991); Kemp et al., "Protein Kinase Recognition Sequence Motifs," Trends in Biochemical Sciences 15(9):342-346 (1990); Sparks et al., "Molecular Basis for Substrate Specificity of Protein Kinases and Phosphatases," Intl. J. Biochem. 18(6):497-504 (1986); Ruzzene et al., "Assay of Protein Kinases and Phosphatases Using Specific Peptide Substrates," Protein Phosphorylation, 2nd Ed., Ed., Hardie, Padua, Italy, pp. 221-253 (1999); Tegge et al., "Analysis of Protein Kinase Substrate Specificity by the Use of Peptide Libraries on Cellulose Paper (SPOT-Method)," Methods in Molecular Biology 87:99-106 (1998); Zhou et al., "The Use of Peptide Library for the Determination of Kinase Peptide Substrates," Methods in Molecular Biology 87:87-98 (1998); Engstroem et al., "Detection and Identification of Substrates for Protein Kinases: Use of Proteins and Synthetic Peptides," Methods in Enzymology 107:130-54 (1984); Casnellie et al., "The Use of Synthetic Peptides

for Defining the Specificity of Tyrosine Protein Kinases," Advances in Enzyme Regulation 22:501-15 (1984); and Fukunaga et al., "Identifying Protein Kinase Substrates by Expression Screening with Solid-Phase Phosphorylation," Protein Phosphorylation, 2nd Ed., Ed., Hardie, Padua, Italy, pp. 291-313 (1999) (copies provided with response to the Office Action dated October 16, 2003).

10. The pentapeptide-based inhibitors, which include an M_1 functional group covalently bound to a pentapeptide sequence, *were synthesized and tested* in two different assays measuring the inhibition constant K_i, or % kinase inhibition, under Literature Mimetic assay conditions (L) and Cellular Mimetic assay conditions (C) to determine suitable M_1 functional groups -those which impart the pentapeptide-based inhibitors with protein kinase inhibitory activity (page 13, line 10 to page 17, line 21). As shown in Tables I-III, 23 different functional groups for M_1 were tested including, but not limited to, phosphonic acid, sulfamic acid, carboxylic acid, aldehyde, amide, and boronic acid functional groups. For example, as shown in Table III and the accompanying description, four (4) different boronic acid functional groups for M_1 were tested under the above two assay conditions and suitable M_1 functional groups were identified (page 17, line 22 to page 22, line 7). Accordingly, the specification discloses identifying functional groups which bind to catalytic residues of a protein kinase (i.e., show protein kinase inhibitory activity) for PKA and $pp60^{c\text{-}src}$ and covalently attaching the first module to a peptide scaffold. Specific structures for functional groups are set forth, as well as a disclosed correlation between their function (binding to catalytic residues of a protein kinase) and structure, based on molecular modeling studies and production and testing of pentapeptide-based inhibitors (page 11, line 1 to page 22, line 7 of the specification). In addition, specific methods for covalently attaching the first module to a peptide scaffold are set forth at page 14, lines 2-5 and page 18, lines 24-27 (references are incorporated by reference at page 65, lines 3-4).

11. The best M_1's (those producing modified peptide inhibitors with good inhibition in the biological assays) are then used to identify the best M_2's. M_2 is the non-peptide molecular fragment that replaces the peptide scaffold. See page 36, lines 6-7 and page 22, line 8 to page 27, line 6 of the specification. The kinase crystal structures and computer modeling are used

for the initial design of the non-peptide M_2 scaffolds. The computer modeling is carried out by starting with the modified peptides containing the best M_1 modules bound in the kinase active site, deleting the peptide scaffold, and building back various candidate M_2 scaffolds starting from the fixed M_1 module still held in its original position in the kinase peptide substrate binding pocket. As such, the second module must have steric and electronic characteristics that mimic the peptide substrate at the phosphorylatable position and adjacent amino acid binding sites (i.e., is capable of occupying the same binding region of the protein kinase as the peptide scaffold). As set forth in the specification, kinase crystal structures are used to design candidate second modules that are subsequently tested experimentally (see page 22, line 8 to page 27, line 6 of the specification). For example, indole and naphthalene second modules replace the tyrosine residue and adjacent amino acids in the $pp60^{c\text{-}src}$ peptide substrate in the Examples of the present application. This process is followed by the synthesis and biological testing of the M_2 scaffolds while attached to the best M_1 modules identified above that the computer modeling identifies as the most promising. The M_2 design process is illustrated in Figures 6 and 7 in the patent application. Examples of M_2 modules that have been validated by biological assays were provided in Table IV of the patent application. A number of examples of non-peptide M_2 scaffolds attached to a variety of good M_1 modules identified as described above were described in the application, including naphthalene, benzofuran , benzothiophene, isoquinoline, indole, and biphenyl. Thus, the specification provides the skilled artisan with specific examples: how good M_1 modules are identified, and how they are subsequently used to identify good M_2 modules. In particular, at page 22, line 8 to page 25, line 13 of the specification, at least one second module (*i.e.*, naphthalene, isoquinoline, or indole) is substituted for the peptide scaffold in molecular modeling studies using the M_1 (first) modules (*e.g.*, boronic acid, phosphonate, and sulfamic acid) previously identified. Next, combinations of the at least one first module covalently attached to at least one second module are produced and tested for protein kinase inhibition (page 25, line 14 to page 27, line 6 of the specification). Moreover, detailed examples and procedures for producing protein kinase inhibitors in which a second module, *e.g.*, naphthalene or indole, is substituted for a peptide scaffold are set forth at page 40, line 16 to

page 61, line 5. In particular, in Example 1 of the specification (page 40, line 16 to page 46, line 23), combinations of a first module (i.e., OH) covalently attached to at least one second module (i.e., naphthalene) are produced, wherein the second module (i.e., naphthalene) is substituted for a peptide scaffold in molecular modeling studies (page 40, lines 16-28). In Examples 2-4 (page 46, line 25 to page 61, line 5) of the specification, combinations of a first module (e.g., OH, boronic acid, and phosphonic acid) covalently attached to at least one second module (i.e., indole) are produced, wherein the second module (i.e., indole) is substituted for a peptide scaffold used in molecular modeling studies (page 47, lines 5-15).

12. In the next step of the method of the invention, the potency and specificity of the compounds are increased by adding back some of the side chains that are similar to those that were present in the original peptide scaffold. This is done to increase the binding affinity of the inhibitor for the target kinase and as well as its selectivity for the particular kinase one is designing inhibitors for relative to other kinases. Specific examples of compounds with combined M_1 and M_2 modules, wherein side chains were added for specificity are given in Table V of the patent application. Again, the method calls for the compounds to be modeled, then functionally assayed by measuring the % kinase inhibition.

13. A final optimization step optionally involves the use of combinatorial chemistry to synthesize many of the compounds that contain various combinations of the best M_1's with the best M_2's, and by optimizing the side chains added back, and/or increasing the number of side chains that are added back. One can also synthesize these combinations of M_1's, M_2's with the side chains by traditional organic synthesis techniques, albeit in a less efficient manner. The inventors have now used the method to generate combinatorial libraries that show high "hit rates", meaning that the percent of the library that are good kinase inhibitors is higher than that in a random library. Some examples are shown in Table VIII of co-pending application USSN10/277,217 (Publication number US20030166615). This table is attached hereto as Appendix B.

14. Because the specification contains explicit guidance about how to perform the claimed methods, and numerous examples of compounds generated according to these methods, I

disagree with the Examiner that the claimed method lacks adequate written description and enablement.

15. For all the foregoing reasons, I believe that the Examiner should withdraw the rejections and allow the pending claims.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

David G. Hangauer, Jr.

Signed at Buffalo, New York
this 22 day of December, 2004

Appendix A

The overall modular, rational, design method was outlined in Figure 1 of the patent application. In order to make the method easier to understand, Figure 1 is divided into individual steps: each step is explained, and examples of each from the patent application are presented.

A) M_1 identification:

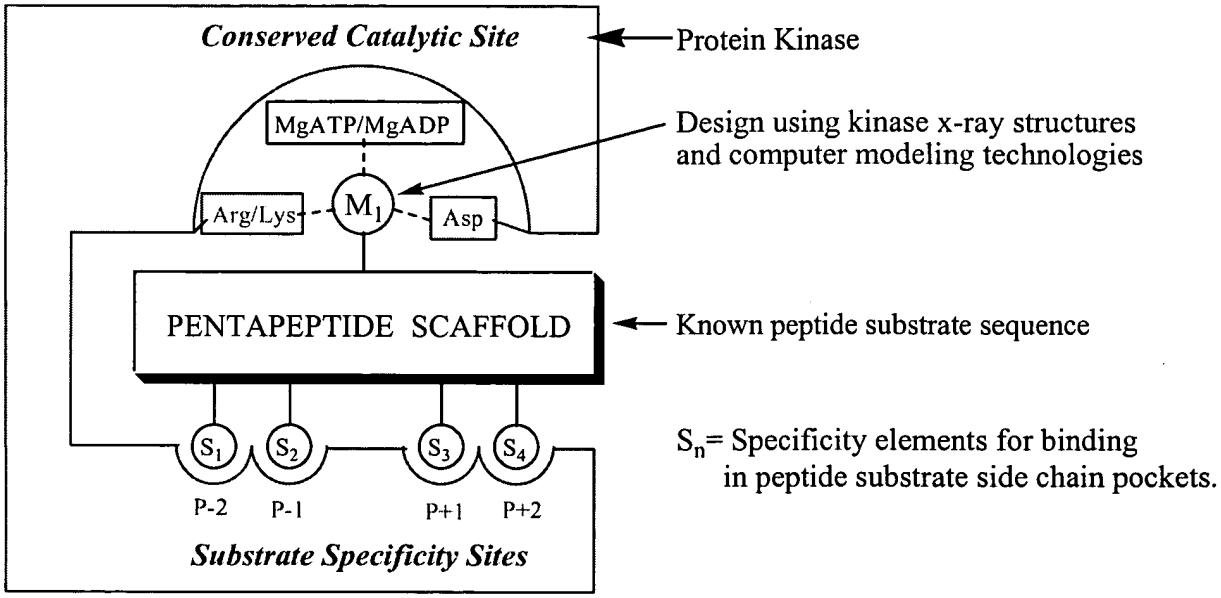
First, good first modules (M_1) are identified. To do this one starts with a known peptide substrate sequence from the literature, or from standard peptide substrate experiments one can carry out, and then synthesizes a small peptide substrate sequence (often with five amino acids, *i.e.* a pentapeptide) wherein the side chain hydroxyl (OH) that is normally phosphorylated in the natural kinase reaction is replaced with various molecular fragments (M_1) that are designed to interact with the conserved catalytic residues of the kinase enzyme, and the co-substrate ATP, or the reaction product ADP, in the enzyme active site. This reaction converts the peptide substrate into a modified peptide that is now an *inhibitor* of the kinase. The conserved catalytic residues are mainly arginine and aspartic acid for tyrosine kinases or lysine and aspartic acid for serine kinases as illustrated in Figure A below.

Suitable M_1 functional groups are designed using available x-ray structural data for kinases and computer modeling studies. The peptide substrate is placed in the peptide binding site of the kinase, the substrate OH (that is normally phosphorylated) is then converted, by computer modeling, to a variety of other molecular fragments (M_1s), and the ability of these fragments to bind to the conserved catalytic residues and ATP or ADP is evaluated using various known computer analyses. This is illustrated in the patent application in Figure 3.

Not all M_1 molecular fragments that look promising using computer studies will provide modified peptides with good inhibition, so these compounds are then synthesized and tested in an enzyme inhibition assay. Thus, the initial step of the method of the invention involves computer modeling studies, synthesis of the modified peptides, and biological testing of these modified peptides.

Note that in figure A, the side chains of the unmodified natural amino acids in the peptide substrate fit into their normal binding pockets that are labeled as Substrate Specificity Sites P-2 through P+2 in Figure A.

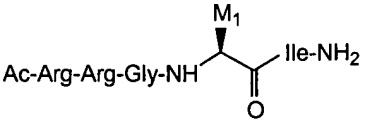
Figure A



Examples of M1 groups identified in this way were given in Table I of the application for the serine kinase PKA and in Table II of the application for the tyrosine kinase Src. These Tables are reproduced below. Note that these modified peptides were synthesized and their biological activity (as measured by the inhibition constant K_i or % inhibition) were measured under two types of biological assay conditions (Literature Mimetic or Cellular Mimetic) with the results as indicated.

TABLE I

INITIAL M_1 SCREENING RESULTS WHILE APPENDED TO THE PKA PENTAPEPTDE SCAFFOLD



---- = Attachment Point

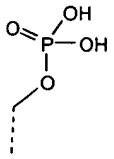
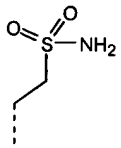
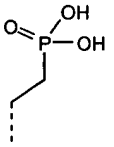
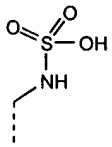
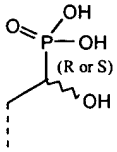
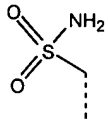
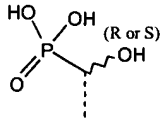
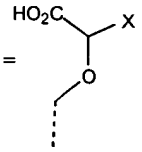
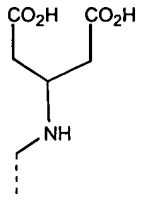
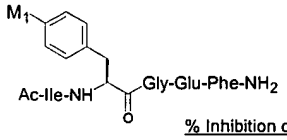
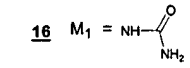
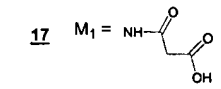
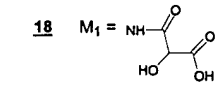
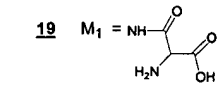
	K_i (μM), (Conditions*) * L=Literature Mimetic C=Cellular Mimetic		K_i (μM), (Conditions*) * L=Literature Mimetic C=Cellular Mimetic	
1 M_1 = (End Product Inhibitor) 	5 (L) 542 (C)	108 X	**7** M_1 = 	300 (L) 2400 (C)	8 X
2 M_1 = 	76 (L) NT (C)		**8** M_1 = 	0.16 (L) 5 (C)	31 X
3 M_1 = 	18 (L)-Diastereomer A 72 (L)-Diastereomer B NT (C)		**9** M_1 = 	250 (L) 2100 (C)	8 X
4 M_1 = 	4 (L)-Diastereomer A 20 (L)-Diastereomer B 171 (C)-Diastereomer A 1510 (C)-Diastereomer B	43 X	**10** M_1 = 	38 (L) 115 (C)	3 X
M_1 = 			**11** M_1 = 	45 (L) NT (C)	
5 X= H	28 (L) 780 (C)	29 X			
6 X= CO_2H	6 (L) 450 (C)	75 X			

TABLE II
INITIAL M_1 SCREENING RESULTS WHILE APPENDED TO THE SRC PENTAPEPTIDE SCAFFOLD



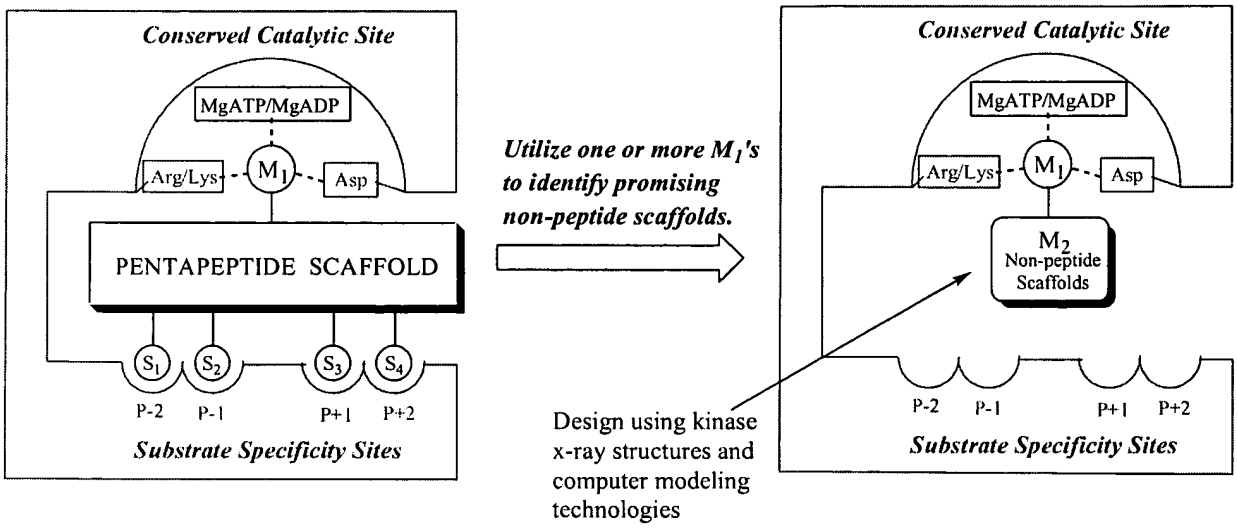
Inhibitor (1 mM)	% Inhibition of 2 mM RR-src phosphorylation by src Assay Conditions: Literature Mimetic	Cellular Mimetic
12 M_1 = 	36	0
13 M_1 = 	51	0
14 M_1 = 	83	88
15 M_1 = 	68	59

Inhibitor (1 mM)	Literature Mimetic	Cellular Mimetic
16 M_1 = 	60	8
17 M_1 = 	20	28
18 M_1 = 	64	5
19 M_1 = 	24	0

B) M_2 identification:

After using the peptide substrate sequence as a scaffold from which various candidate M_1's were experimentally tested, the best M_1's (meaning those giving modified peptide inhibitors with good inhibition in the biological assays) are then used to identify the best M_2's. M_2 is the non-peptide molecular fragment that replaces the peptide scaffold used in beginning the method above. One wants to replace the peptide scaffold with a non-peptide M_2 scaffold because peptides typically are not good for use as oral drugs. As was the case for obtaining M_1's, the kinase crystal structures and computer modeling are used for the initial design of the non-peptide M_2 scaffolds. The computer modeling can be carried out by starting with the modified peptides containing the best M_1 modules bound in the kinase active site, deleting the peptide scaffold, and building back various candidate M_2 scaffolds starting from the fixed M_1 module still held in its original position in the kinase peptide substrate binding pocket. This is process is followed by the synthesis and biological testing of the M_2 scaffolds while attached to the best M_1 modules identified above that the computer modeling identifies as the most promising. This process is illustrated in Figure B.

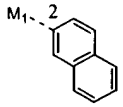
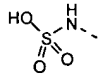
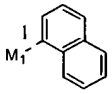
Figure B

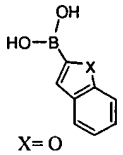
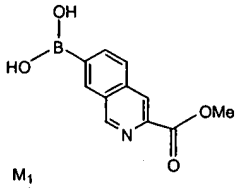
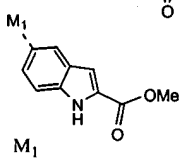
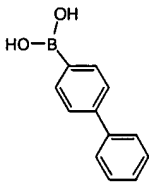
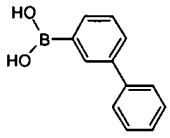


This M_2 design process was also illustrated in Figures 6 and 7 in the patent application. Examples of M_2 modules that have been validated by biological assays were provided in Table IV of the patent application, which is reproduced below.

TABLE IV

INITIAL STEP 1 RESULTS
% SRC INHIBITION IN CELLULAR MIMETIC ASSAY

	Inhibitor	% Inhibition of 2 mM RR-src at Inhibitor Concentration ()
	 --- = Attaching bond.	
	M_1	
27		59 (1 mM) 13 (100 μM) IC_{50}=950 μM *NON-ATP COMPETITIVE* K_i= 554 μM
28		31 (1 mM) IC_{50}=1.6 mM *NON-ATP* K_i=963 μM *COMPETITIVE*
29		0 (1 mM)
30		14 (1 mM)
31		0 (100 μM)
		
	M_1	
32		0 (100 μM)
33		1 (1 mM)
34		0 (100 μM)

	Inhibitor		% Inhibition of 2 mM RR-src at Inhibitor Concentration ()
			
35	X= O		10 (100 μM)
36	X= S		12 (100 μM)
37			13 (500 μM)
			
	M_1		
38		*NON-ATP COMPETITIVE*	62 (500 μM)
39			11 (500 μM)
40			13 (100 μM)
41			14 (100 μM)

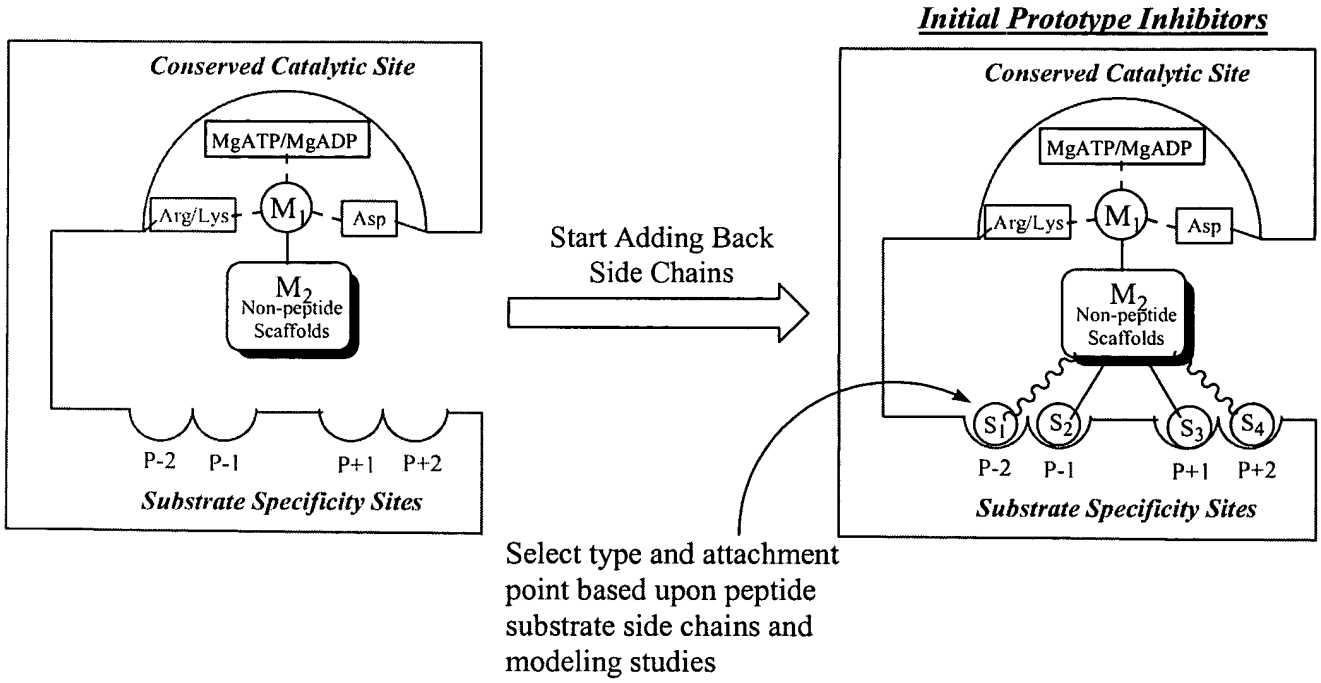
Note that in Table IV are a number of examples of non-peptide M_2 scaffolds attached to a variety of good M_1 modules identified as described above. Compounds **27** through **34** show the naphthalene M_2 wherein M_1 is best attached to carbon atom labeled the 2 position. Compounds **35** & **36** show that a benzofuran or a benzothiophene, respectively, can serve as a good M_2. Compound **37** demonstrates that an isoquinoline can serve as a good M_2. Compounds **38** & **39** show that an indole can serve as a good M_2. Compounds **40** & **41** show that a biphenyl can serve as a good M_2. So the Method as described thus far teaches, and enables with specific examples,

how good M_1 modules can be identified, and how they can be subsequently used to identify good M_2 modules and be combined with them.

C) Increase Specificty:

Once good combinations of M_1 and M_2 have been designed from the kinase crystal structure, synthesized and experimentally tested in biological assays to identify those that are actually good inhibitors, the next step is carried out to initially increase these compounds potency and specificity. This step is illustrated in Figure C below.

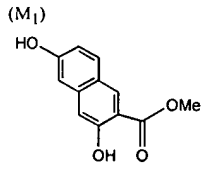
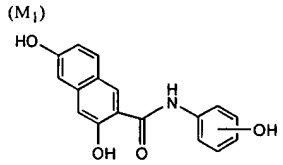
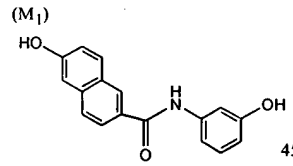
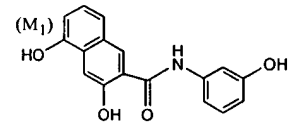
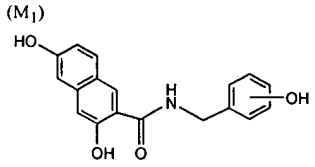
Figure C

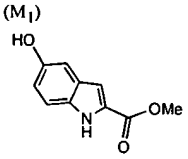
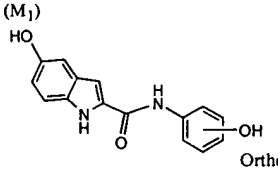
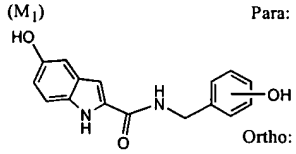
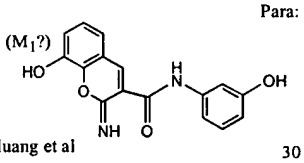
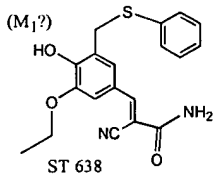
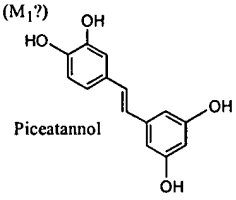


In this step, some of the side chains that are similar to those that were present in the original peptide scaffold are added back. This is done to increase the binding affinity of the inhibitor for the target kinase and as well as its selectivitiy for this kinase as opposed to other kinases. Examples of these combined M_1 & M_2 modules wherein side chains were being added were given in Table V of the patent application, and reproduced below.

TABLE V

INITIAL STEP 2 RESULTS
% SRC INHIBITION IN CELLULAR MIMETIC ASSAY

Inhibitor	% Inhibition of 2 mM RR-src at Inhibitor Concentration ()
42 	47 (100 μM)
43 	Ortho: 39 (100 μM) Meta: 89 (100 μM) *NON-ATP COMPETITIVE* IC_{50}=18 μM, K_i=10 μM Para: 23 (100 μM)
44 	45 (100 μM)
45 	*NON-ATP COMPETITIVE* 51 (100 μM) IC_{50}=170 μM
46 	Ortho: 42 (100 μM) Meta: In progress Para: 42 (100 μM)

Inhibitor	% Inhibition of 2 mM RR-src at Inhibitor Concentration ()
47 	40 (500 μM)
48 	Ortho: 43 (100 μM) Meta: 30 (100 μM) Para: 45 (100 μM)
49 	Ortho: 24 (100 μM) Meta: In progress Para: 54 (100 μM)
50  Huang et al	30 (100 μM) Lit. IC_{50}= 118 nM
51  ST 638	37 (100 μM) Lit. IC_{50}=18 μM
52  Piceatannol	41 (100 μM) Lit. IC_{50} = 66 μM for $p56^{lck}$

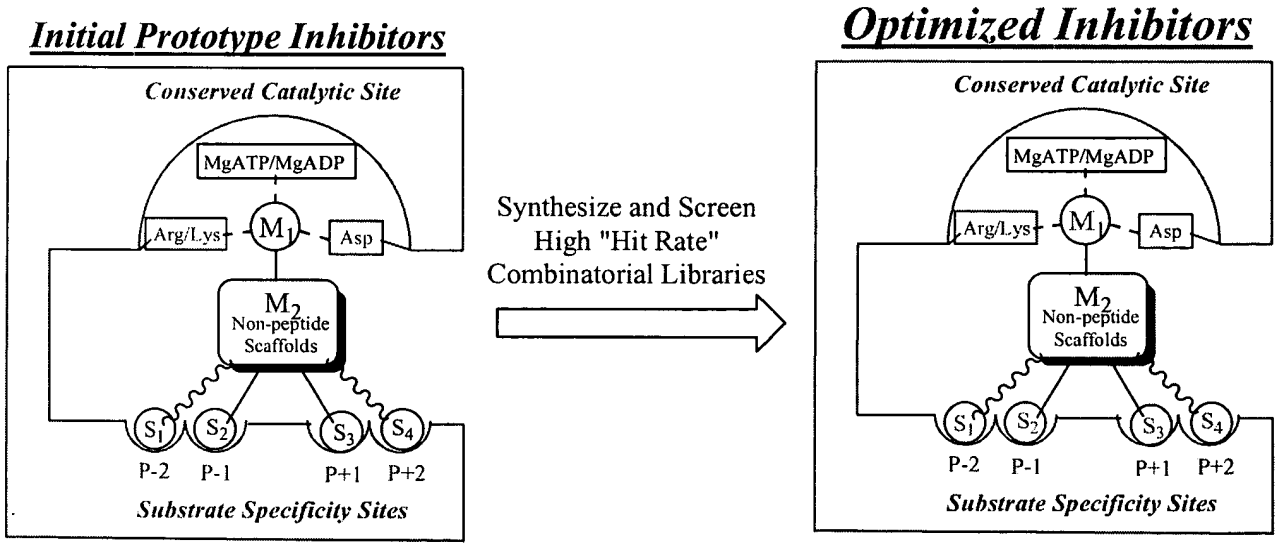
Note that the naphthalene M_2 inhibitors **42** through **46** shown in Table V are utilizing an OH as M_1 and are more potent inhibitors than the M_2 naphthalene inhibitors shown earlier in Table IV. Likewise the indole M_2 inhibitors shown in Table V are utilizing an OH as M_1 are more potent inhibitors than the M_2 indole inhibitors **47** & **48** shown earlier in Table IV. So, once

again, the patent teaches how to initially increase the potency of these inhibitors, and enables this teaching with specific examples.

D) Optimization:

The next step of the Method is basically a final optimization step. This can be efficiently done by using combinatorial chemistry to synthesize all, or many, of the compounds that contain various combinations of the best M_1's with the best M_2's, and by optimizing the side chains added back, and/or increasing the number of side chains that are added back. This step is illustrated in Figure D below.

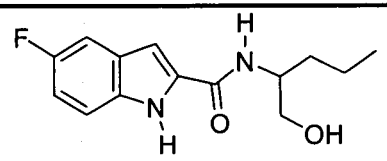
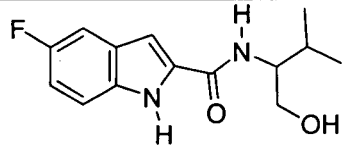
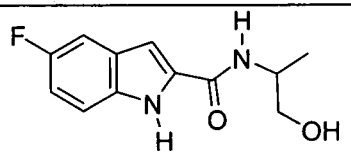
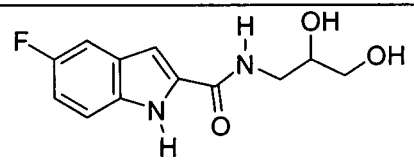
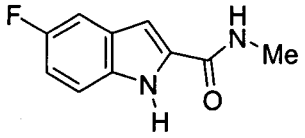
Figure D

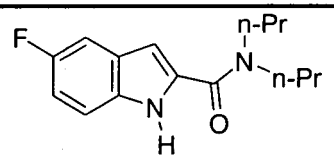
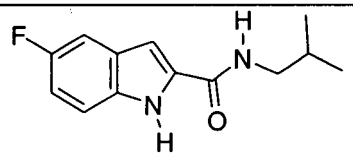
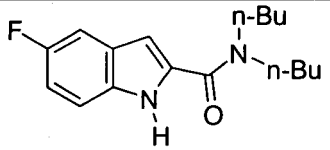
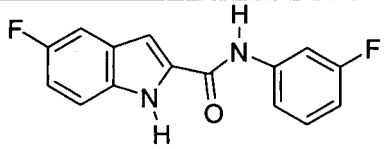
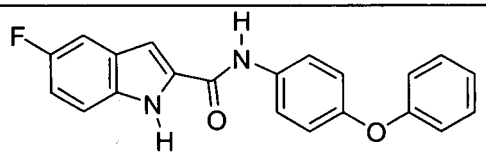
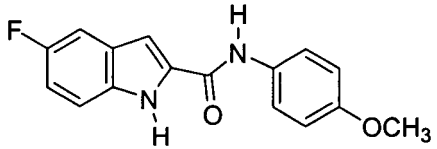
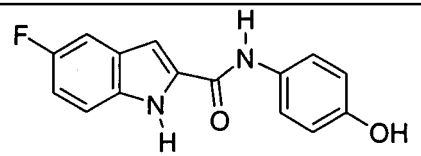


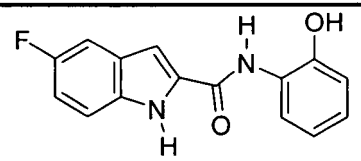
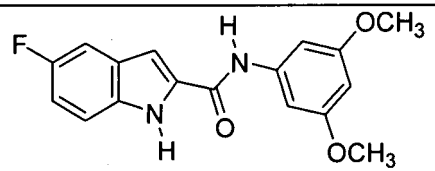
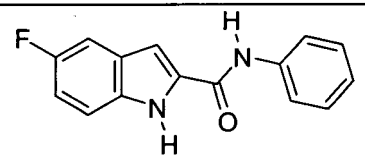
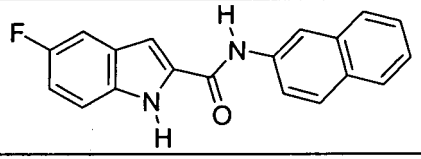
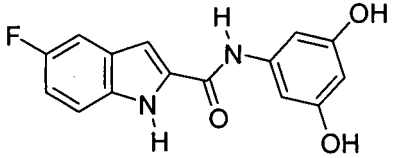
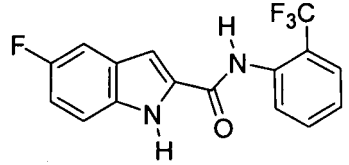
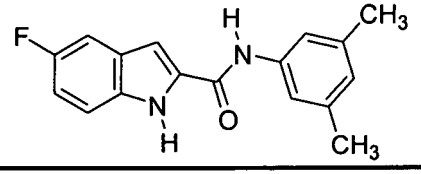
What makes the Method of the invention so powerful is that this final optimization step is focused on a limited number of possible compounds that have a high likelihood of being good kinase inhibitors. This results in combinatorial libraries that show high "hit rates", meaning that the percent of the library that are good kinase inhibitors is higher than that in a random library. The alternative to using this Method is to simply synthesize compounds at random and then screen them against the target kinase. This is a very impractical approach since the number of randomly possible compounds is far beyond the capability of any laboratory to synthesize. The number of possible drug-like small compounds has been variously estimated to be somewhere in the range of 10^{60}or greater. There is not enough matter within the earth to synthesize a 1 mg sample of each of these compounds, and the cost of synthesis and biological testing would be prohibitive.

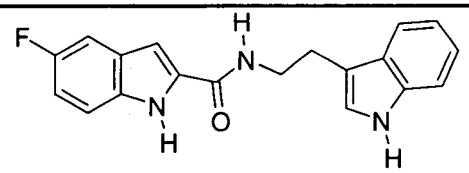
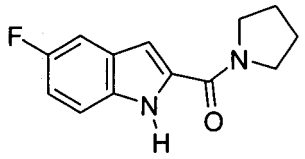
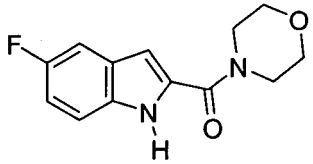
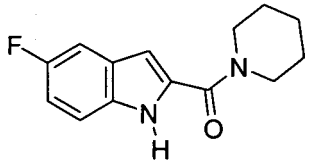
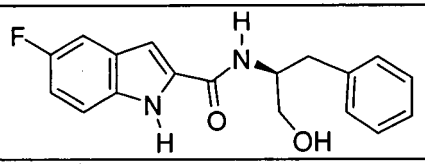
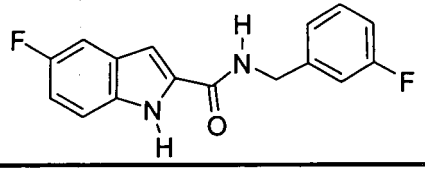
Appendix B

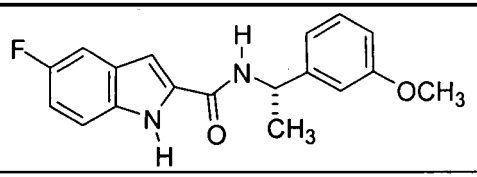
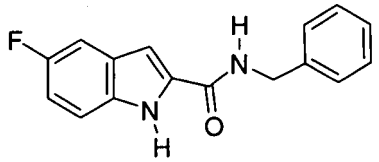
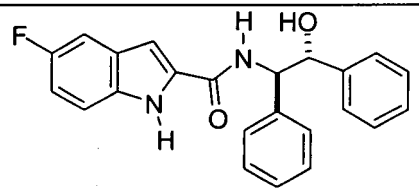
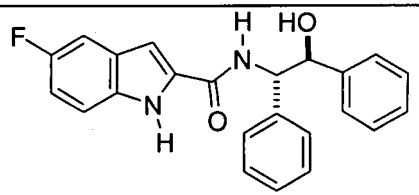
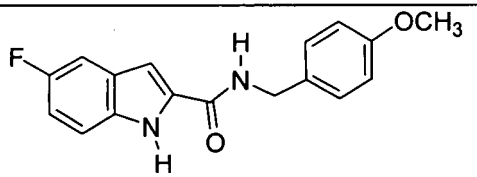
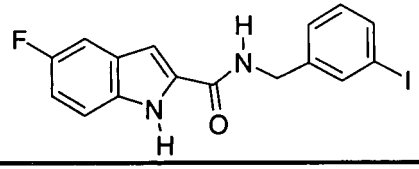
INHIBITION OF EGFRPTK, p56 lck, p55 fyn, and PTP-1B

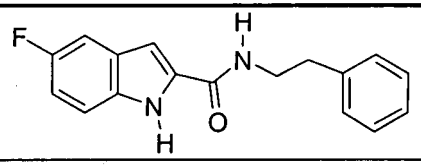
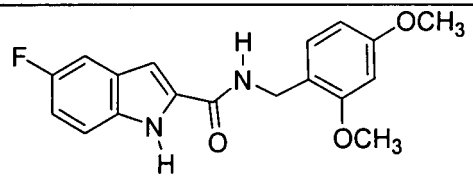
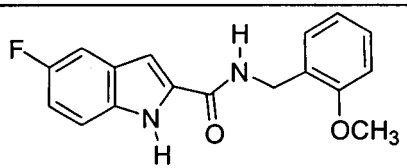
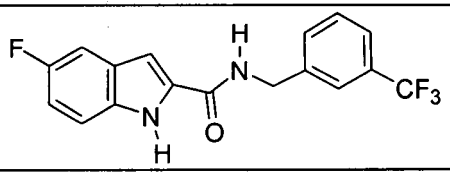
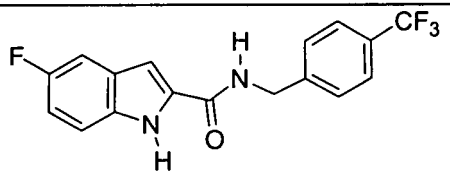
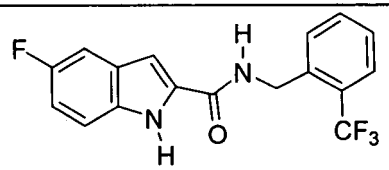
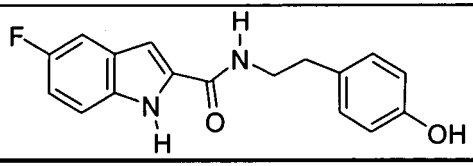
Structure	MW	Compound Code	PTP-1B @ 10μm	EGFRTK @ 10μm	p56 Lck @ 10μm	p55 fyn @ 10μm
	264.3	1b				
	264.3	1c				
	236.2	1d				
	252.2	1e				
	192.2	1f				

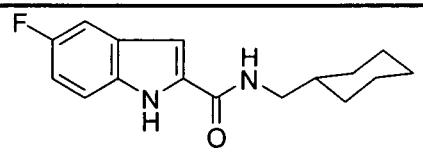
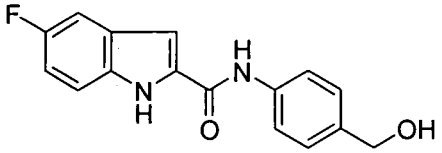
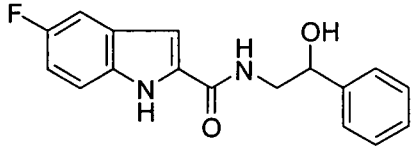
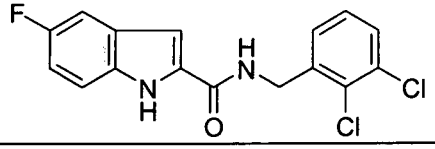
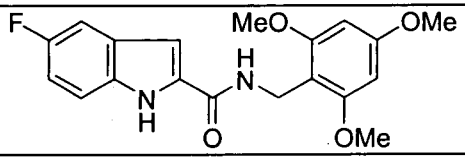
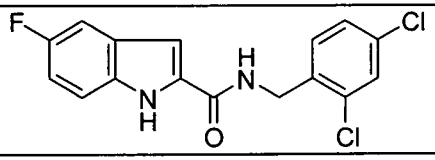
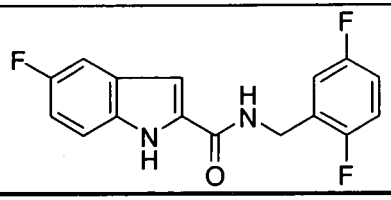
	262.3	**1g**				19
	234.3	**1h**				
	290.4	**1i**				
	272.3	**1j**				
	346.4	**1k**				13
	284.3	**1l**				
	270.3	**1m**				

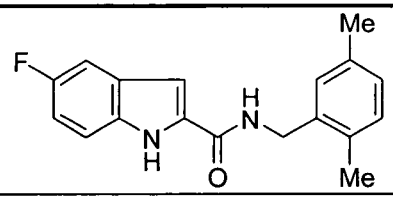
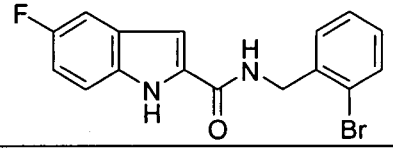
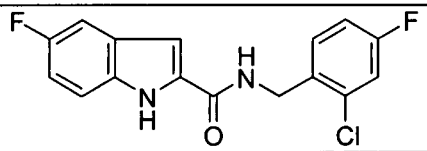
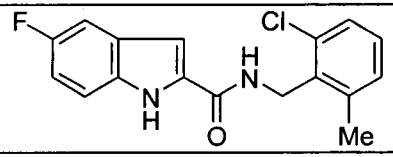
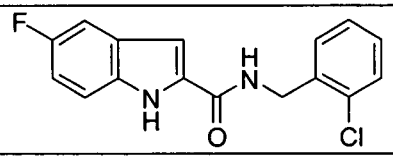
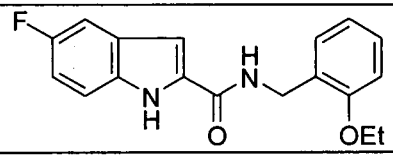
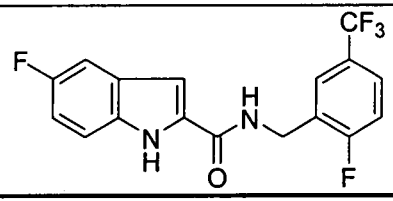
	270.3	**1n**			12	
	314.3	**1o**				
	254.3	**1p**				
	304.3	**1q**				
	286.3	**1r**			11	
	322.3	**1s**				
	282.3	**1t**				11

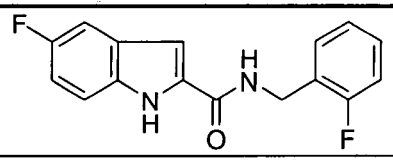
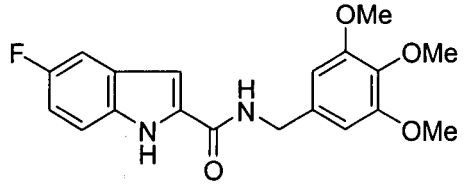
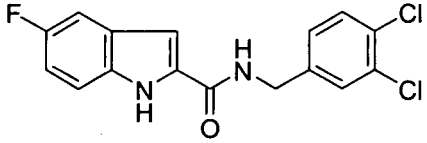
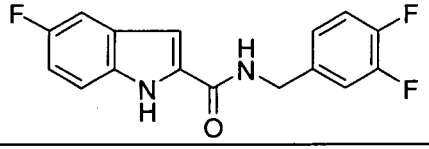
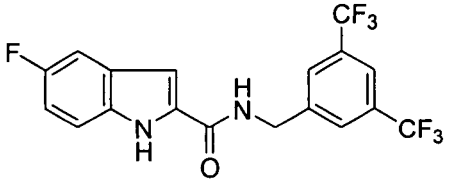
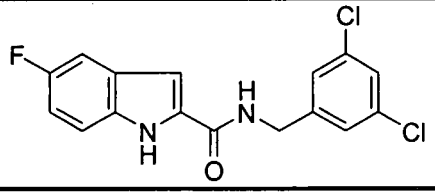
	321.4	**1u**				10
	232.3	**1v**				
	248.3	**1w**				10
	246.3	**1x**				
	312.3	**1y**				
	286.3	**1z**		26		

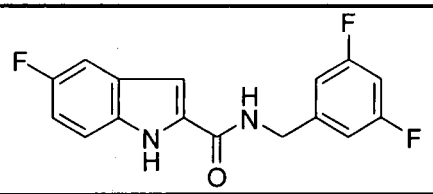
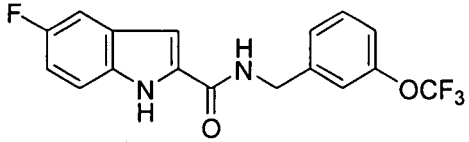
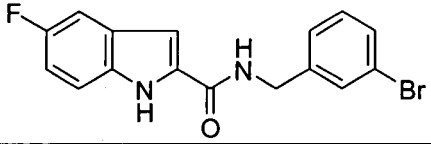
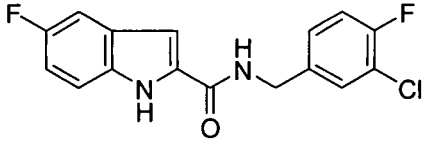
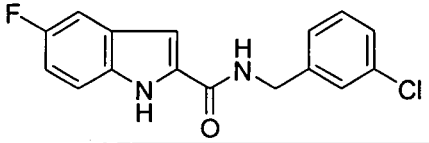
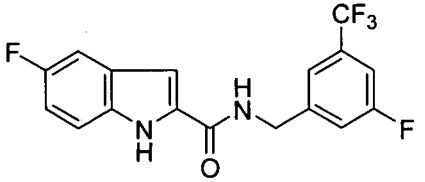
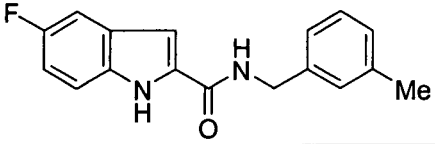
	312.3	**1aa**		12		10
	268.3	**1bb**		19		
	374.4	**1cc**		19		
	374.4	**1dd**		41		
	298.3	**1ee**		16		
	394.2	**1ff**		24		

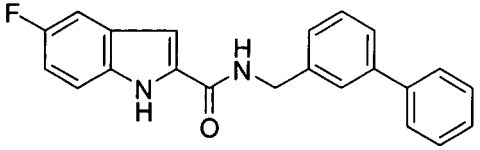
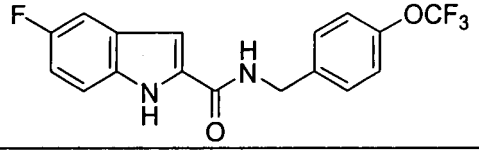
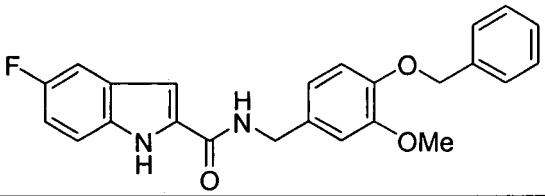
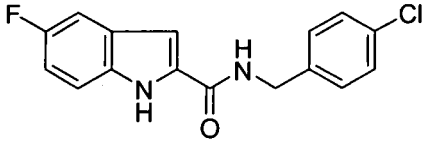
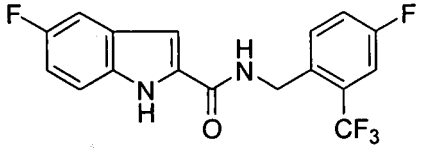
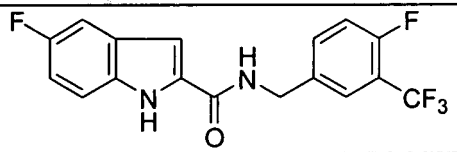
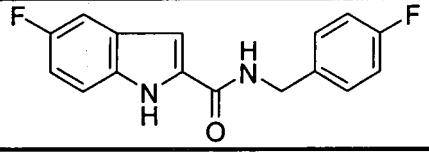
	282.3	1gg				
	328.3	1hh				
	298.3	1ii				
	336.3	1jj				18
	336.3	1kk				
	336.3	1ll				
	298.3	1mm				

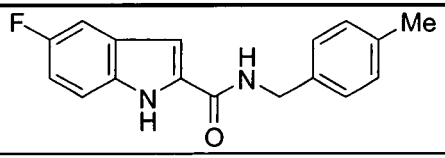
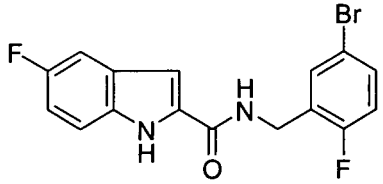
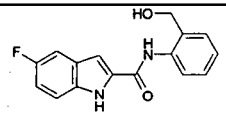
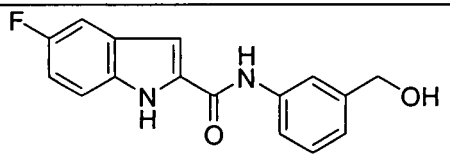
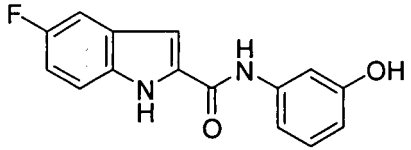
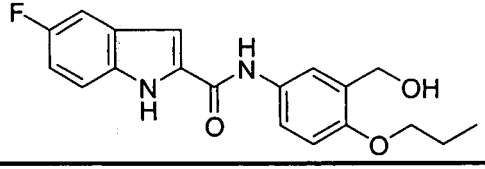
	274.3	**1nn**				
	284.3	**1oo**				17
	298.3	**1pp**				
	337.2	**1qq**				
	358.4	**1rr**			12	
	337.2	**1ss**	12			
	304.3	**1tt**				

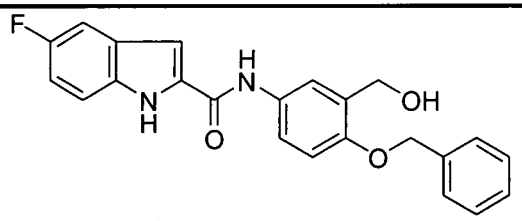
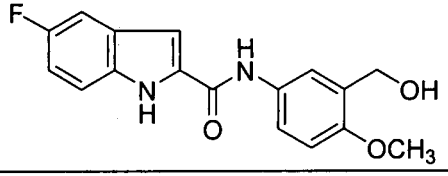
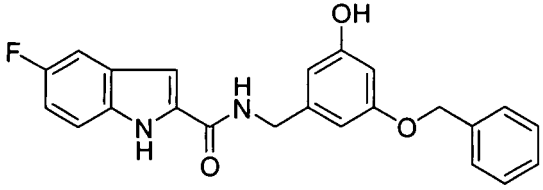
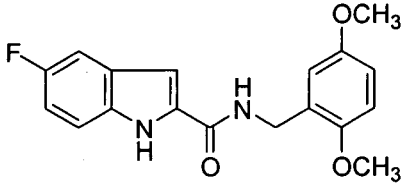
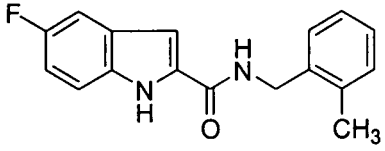
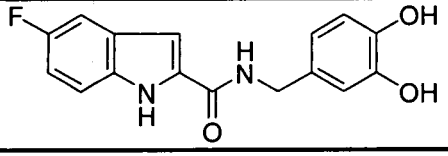
	296.3	**1uu**				
	347.2	**1vv**				
	320.7	**1ww**				
	316.8	**1xx**				14
	302.7	**1yy**	10			12
	312.3	**1zz**				
	354.3	**1aaa**	12			

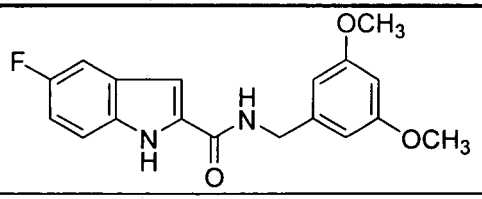
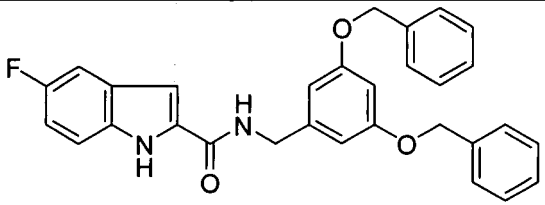
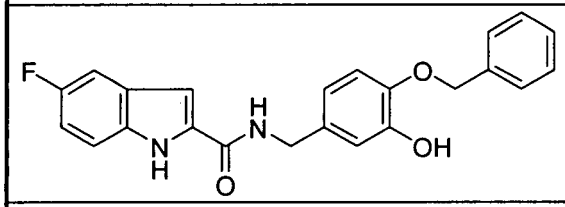
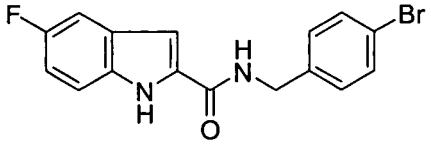
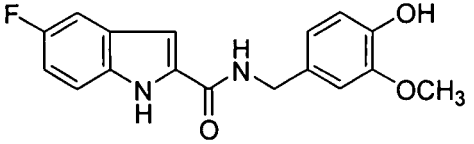
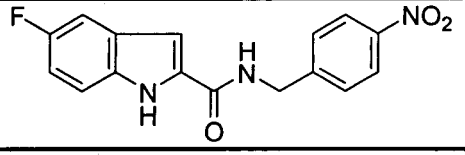
	286.3	**1bbb**				
	358.4	**1ccc**				
	337.2	**1ddd**				
	304.3	**1eee**				
	404.3	**1fff**				
	337.2	**1ggg**				

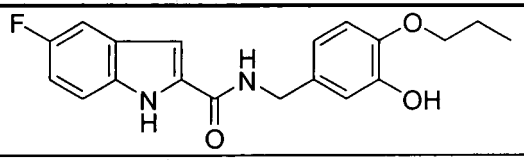
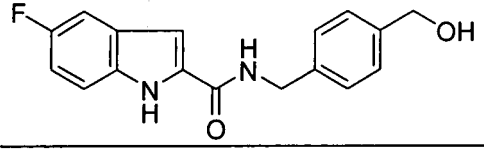
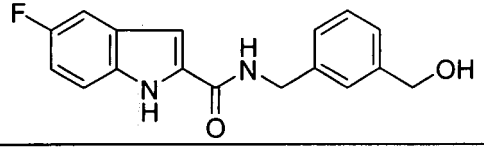
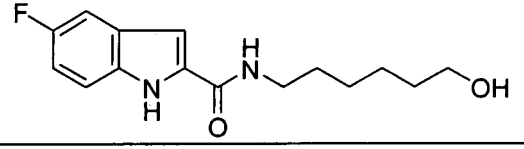
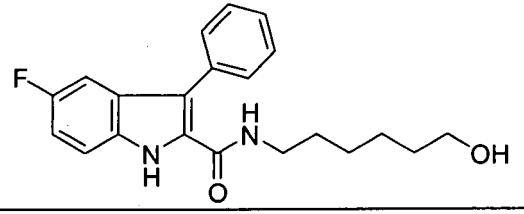
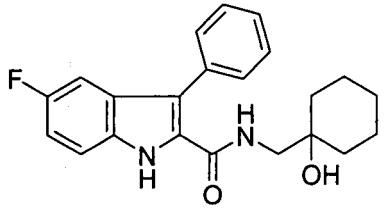
	304.3	**1hhh**				
	352.3	**1iii**				
	347.2	**1jjj**				
	320.7	**1kkk**				
	302.7	**1lll**				
	354.3	**1mmm**				14
	282.3	**1nnn**				

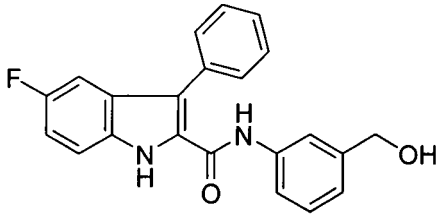
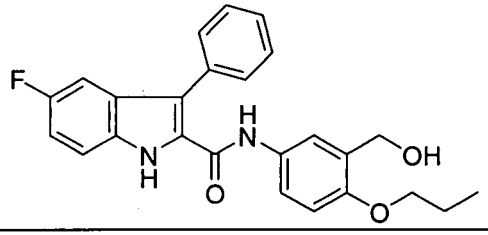
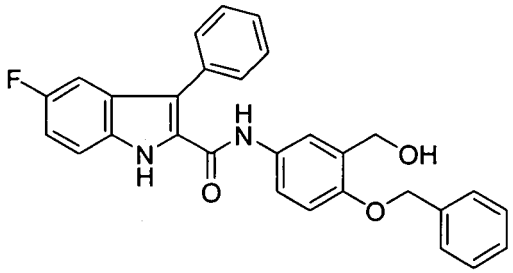
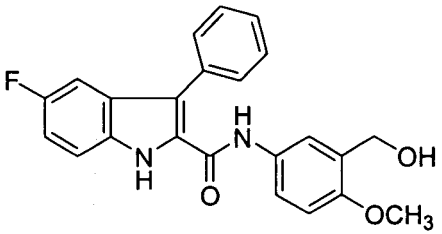
	344.4	**1ooo**				
	352.3	**1ppp**				
	404.4	**1qqq**				11
	302.7	**1rrr**				15
	354.3	**1sss**				
	354.3	**1ttt**				
	286.3	**1uuu**	13			16

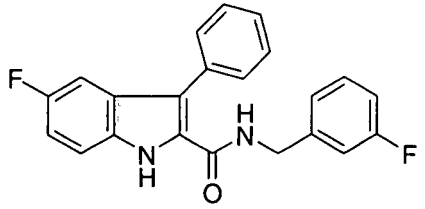
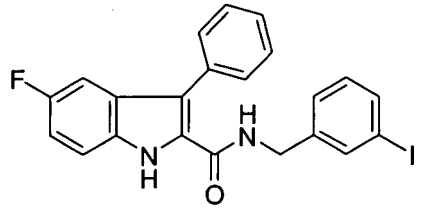
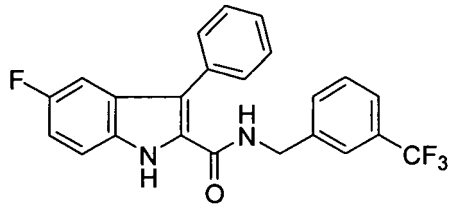
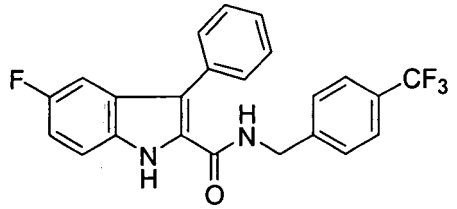
	282.3	**1vvv**				
	365.2	**1www**				
	284.3	**1xxx**	12			
	284.3	**1yyy**		11		
	270.3	**1zzz**				
	342.4	**1aaaa**				

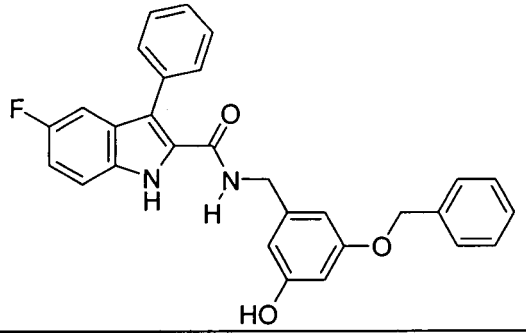
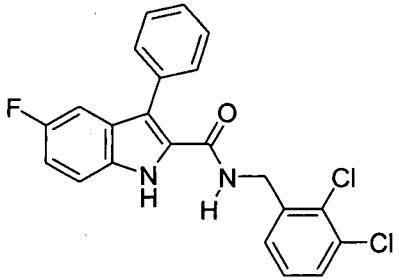
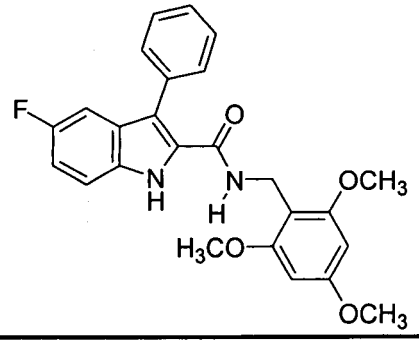
	390.4	**1bbbb**				
	314.3	**1cccc**	20	19		
	390.4	**1dddd**	16			
	328.3	**1eeee**				
	282.3	**1ffff**		12		
	300.3	**1gggg**		25		

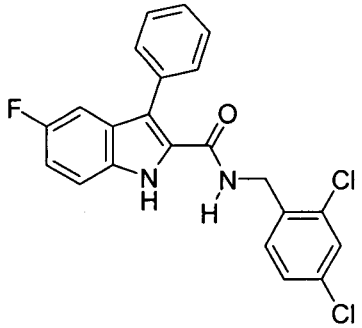
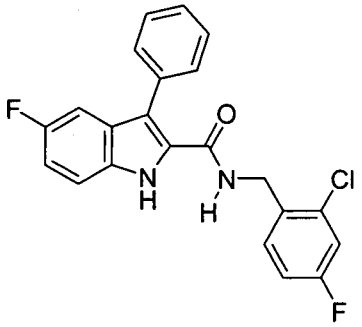
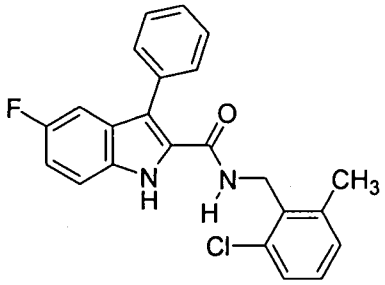
	328.3	**1hhhh**	17			
	480.5	**1iiii**		12		
	390.4	**1jjjj**	15			
	347.2	**1kkkk**		30		
	314.3	**1llll**				
	313.3	**1mmmm**				29

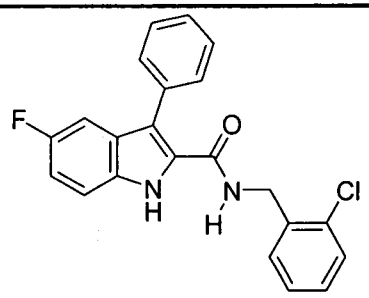
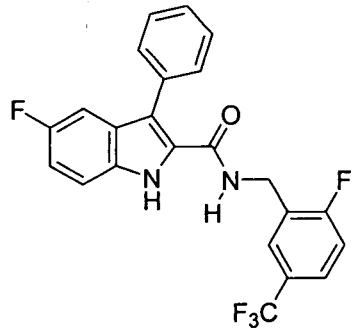
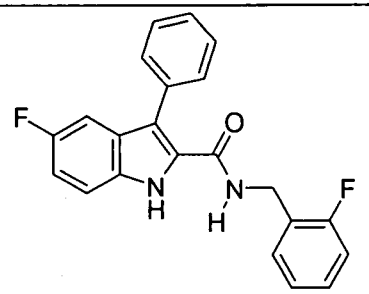
	342.4	**1nnnn**		17		11
	298.3	**1oooo**		33	10	
	298.3	**1pppp**				
	278.3	**1qqqq**		18		
	354.4	**2a**				
	366.4	**2b**		19		13

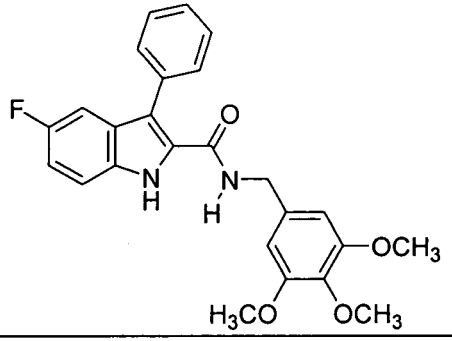
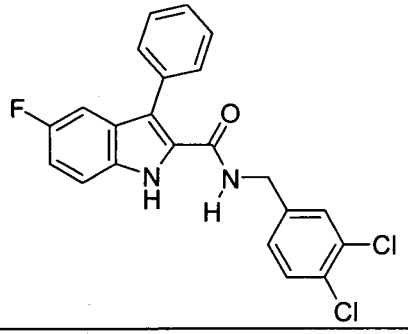
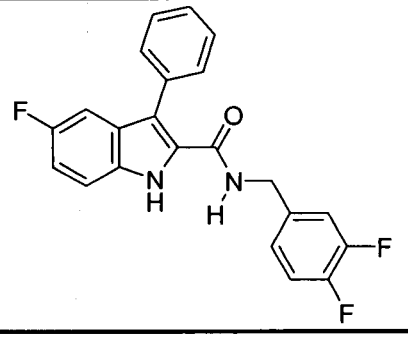
	360.4	**2c**				
	418.5	**2d**		23		
	466.5	**2e**		10		
	390.4	**2f**		18		11

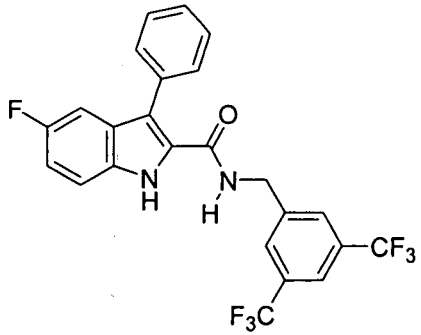
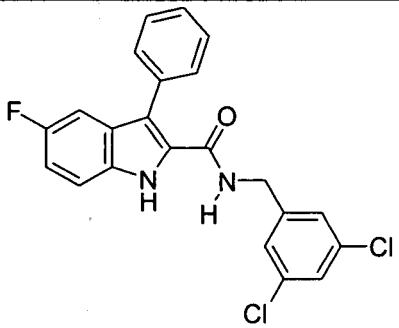
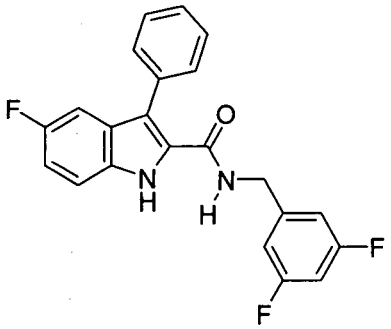
	362.4	**2g**				
	470.3	**2h**				
	412.4	**2i**				
	412.4	**2j**		20		

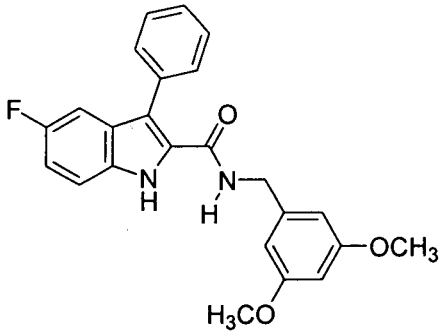
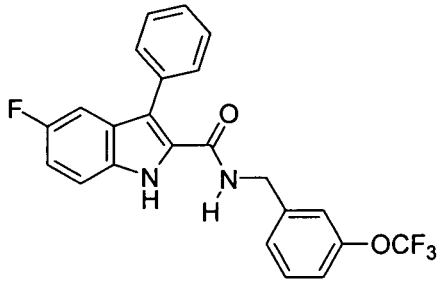
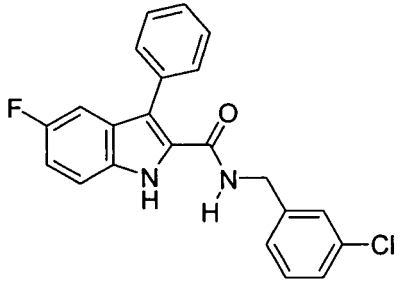
	466.5	**2k**				
	413.3	**2l**				
	434.5	**2m**				

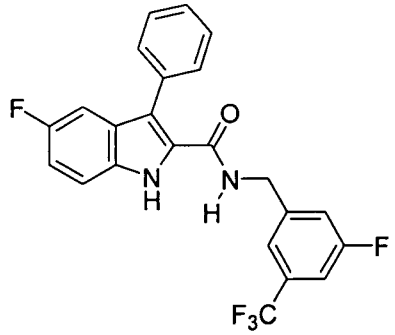
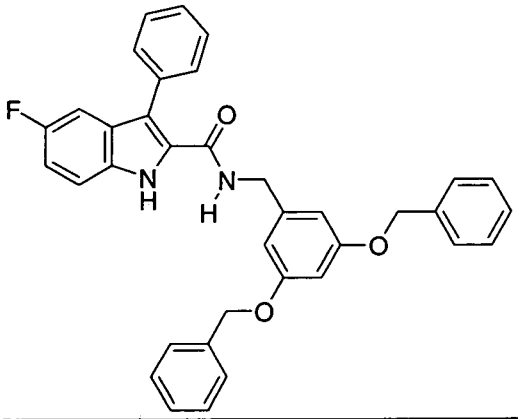
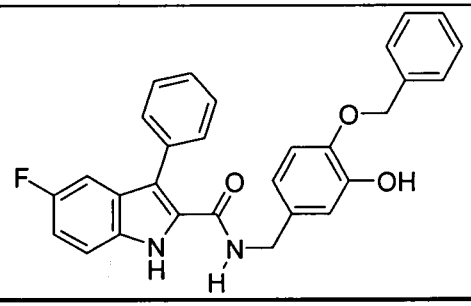
	413.3	**2n**				
	396.8	**2o**				12
	392.9	**2p**				

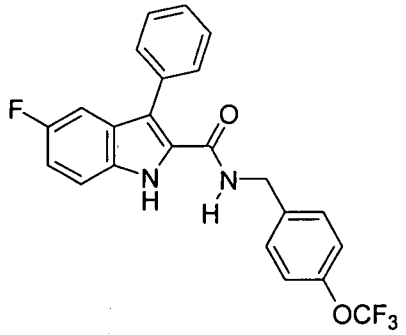
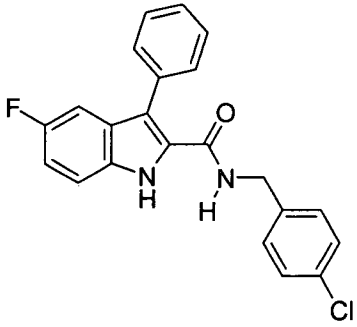
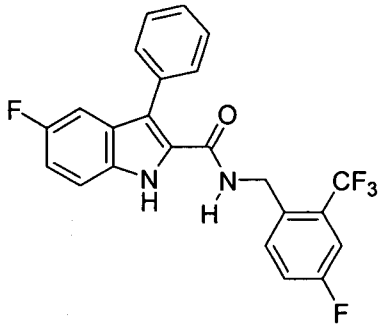
	378.8	**2q**				
	430.4	**2r**				
	362.4	**2s**		33	10	11

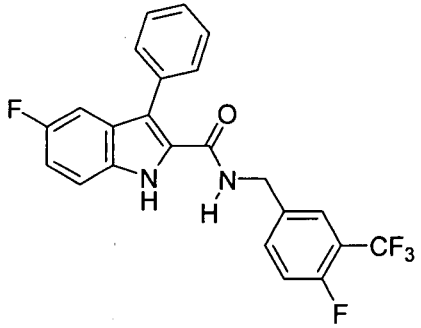
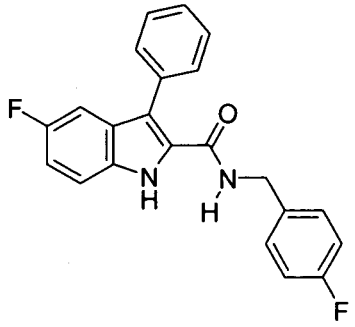
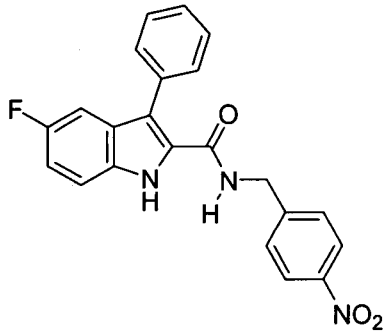
	434.5	**2t**				
	413.3	**2u**				
	380.4	**2v**				

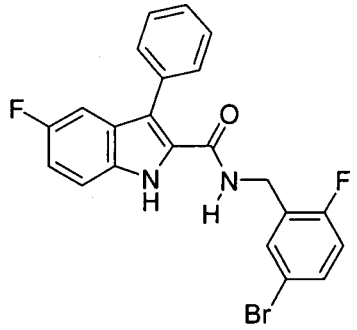
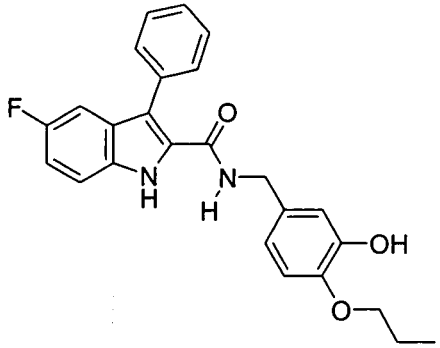
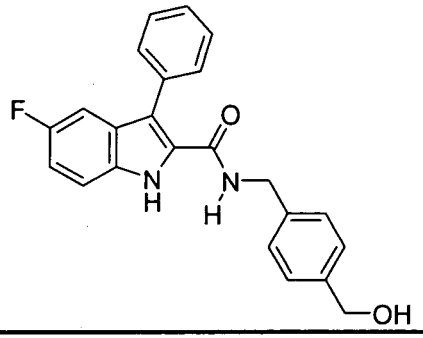
	480.4	**2w**	12			
	413.3	**2x**				
	380.4	**2y**		20		

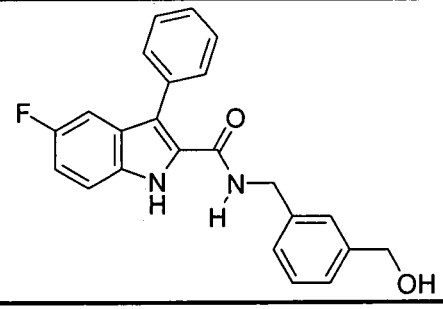
	404.4	**2z**				
	428.4	**2aa**				
	378.8	**2bb**				

	430.4	**2cc**				
	556.6	**2dd**				
	466.5	**2ee**				

	428.4	**2ff**				
	378.8	**2gg**	12			
	430.4	**2hh**		12		

	430.4	**2ii**				
	362.4	**2jj**				
	389.4	**2kk**				24

	441.3	**2ll**		10		
	418.5	**2mm**				
	374.4	**2nn**				

	374.4	2oo				